



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/743,163	12/22/2003	Mehmet Inan	15948Z	7785
23389	7590	12/14/2006		
SCULLY SCOTT MURPHY & PRESSER, PC 400 GARDEN CITY PLAZA SUITE 300 GARDEN CITY, NY 11530				
			EXAMINER DUNSTON, JENNIFER ANN	
			ART UNIT 1636	PAPER NUMBER

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

74

Office Action Summary	Application No.	Applicant(s)	
	10/743,163	INAN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-22 and 24-30 is/are rejected.
- 7) ☒ Claim(s) 23 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 December 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3/06, 1/06, 6/03</u> | 6) <input checked="" type="checkbox"/> Other: <u>Exhibits I-XII</u> |

Art Unit: 1636

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 9/25/2006, in which claims 25-30 were newly added. Currently, claims 1-30 are pending.

Election/Restrictions

The restriction requirement mailed 8/22/2006 has been WITHDRAWN. Currently, claims 1-30 are under consideration.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 5 and 7-22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 5-20 of U.S. Patent No. 6,699,691 (hereinafter the '691 patent).

Art Unit: 1636

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

The instant claims are drawn to or encompass an isolated polynucleotide comprising the sequence of SEQ ID NO: 20. The conflicting claims are drawn to or encompass an isolated polynucleotide consisting of the sequence of SEQ ID NO: 20. The conflicting sequence is identical to the instant sequence. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claim 5 is generic to all that is recited in claim 1 of the '691 patent. That is, claim 1 of the '691 patent falls entirely within the scope of claim 5 of the instant application or, in other words, instant claim 5 is anticipated by claim 1 of the '691 application. Furthermore, instant claims 7-22 are generic to and anticipated by conflicting claims 5-20, respectively.

Thus, the instant claims, if allowed, would extend patent protection of the invention of the '691 patent. Further, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the rights to the '691 invention, then two different assignees would hold patent claims to the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

Art Unit: 1636

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of “under conditions of high stringency” in claims 1-6 renders the claims vague and indefinite because the metes and bounds of what constitutes “high stringency” are unclear. In the specification, there is a discussion of several examples of high stringency conditions, and that such conditions usually involve a combination of salt and temperature conditions at a certain range below T_m , but none of what is stated in this section defines the conditions to a particular set of metes and bounds and thus the metes and bounds are unclear. Examples of particular conditions do not exclude other sets of conditions not exemplified. Thus, it is unclear what all of the conditions are that are encompassed by “high stringency”.

Claims 7-22 depend from any one of claims 1-6 and thus are indefinite for the same reasons as applied to claims 1-6.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

Art Unit: 1636

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claims 26-30 are drawn to an isolated polynucleotide comprising SEQ ID NO: 16 or variant thereof, further comprising multiple copies of SEQ ID NO: 16 (claim 26), multiple copies of SEQ ID NO: 17 (claim 27), multiple copies of SEQ ID NO: 18 (claim 28), multiple copies of SEQ ID NO: 19 (claim 29) or multiple copies of SEQ ID NO: 20 (claim 30).

The response filed 9/25/2006 asserts that support for the amendments can be found within the specification at page 25, lines 5-27 and page 12, lines 15-16. At page 12, lines 15-16, the specification defines the terms “polynucleotide” and “oligonucleotide” to mean a polymeric (2 or more monomers) form of nucleotides of any length, either ribonucleotides or deoxyribonucleotides. The monomers referred to in this definition are clearly nucleotides (page 12, lines 17-21). The monomers are not copies of SEQ ID NO: 16, 17, 18, 19 or 20, and thus this portion of the specification does not provide support for claims 26-30. At page 25, the specification provides support for a regulatory region that comprises “SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, from 1 to about 3 copies of SEQ ID NO: 20, and SEQ ID NO: 21.” This portion of the specification provides support for a single sequence that contains SEQ ID NOS: 16-18 and 21 in addition to 1-3 copies of SEQ ID NO: 20. This one example does not provide support for the genus of polynucleotides comprising SEQ ID NO: 16 (or variant thereof) and multiple copies of SEQ ID NO: 20. Furthermore, there is no support for multiple copies of SEQ ID NO: 17, 18 or 19.

The original specification, drawings and claims were thoroughly reviewed and no support could be found for the amendment. Accordingly, the amendment is a departure from the

Art Unit: 1636

specification and claims as originally filed, and the passages that Applicant has provided do not provide support.

Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to or encompass regulatory regions defined as a fragment, a polynucleotide that hybridizes under "high stringency", and a polynucleotide defined by at least 80% sequence homology the fragment or full-length sequence recited in the claims. Claims 1-6 are drawn to SEQ ID NOS: 16, 17, 18, 19, 20 and 21, respectively. Thus, the rejected claims are drawn to a genus of isolated polynucleotides that are fragments and variants of SEQ ID NO: 16, 17, 18, 19, 20 or 21. The isolated polynucleotides must be capable of functioning as a regulatory region.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The instant specification teaches that the *P. pastoris* AOX1 promoter was known in the prior art (e.g. Stroman et al, US Patent No. 4,855,231, paragraph bridging pages 4-5 of the instant specification; Tschopp et al, cited as reference #27 on the IDS filed 12/22/2003,

Art Unit: 1636

page 34, lines 19-20). The prior art promoter sequence is disclosed in instant SEQ ID NO: 1.

This sequence has been divided into sub-regions A-F (SEQ ID NOS: 16-21, respectively) within the present specification.

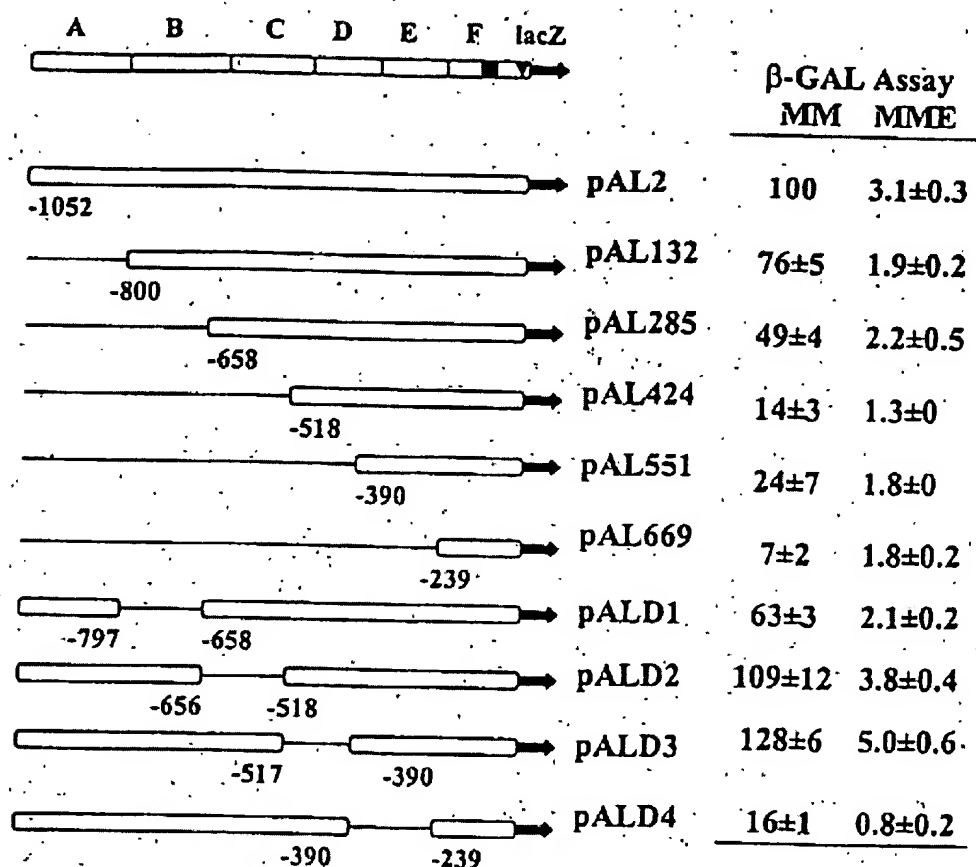


FIGURE 2

The specification describes the regulatory regions A (SEQ ID NO: 16), B (SEQ ID NO: 17), C (SEQ ID NO: 18), D (SEQ ID NO: 19), E (SEQ ID NO: 20) and F (SEQ ID NO: 21). The specification teaches that regions A and C are capable of binding proteins from *P. pastoris* extracts from induced (methanol) and uninduced cells, respectively (e.g. pages 42-43). No description is provided of the specific sequences within A and C bound by the proteins. Thus, the specification does not describe a fragment of A or C that has regulatory function. Further,

Art Unit: 1636

the specification teaches that fragments B, D, E and F did not reveal any DNA-protein complexes (e.g. page 43, lines 8-15).

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of regulatory elements comprising SEQ ID NO: 16, 17, 18, 19, 20 or F, or disclosed combinations thereof. The results are not necessarily predictive of fragments of these sequences or other sequences defined by percent identity, because the necessary transcription factor binding sites required for regulatory function have not been identified. The instant specification teaches that AOX1 and AOX2 are both repressed during growth on glucose, derepressed during carbon limitation, and induced by growth on methanol as the sole carbon source (e.g. page 4, lines 11-16). Even though the promoters are regulated in a similar manner, sequence comparison is insufficient to identify the transcription factor binding sites (partial structures) necessary for promoter function. In fact, the specification teaches that the 5' upstream regulatory regions of AOX1 and AOX2 do not have significant regions of homology (e.g. page 4, lines 11-16). Moreover, the specification teaches that AOX1 has only 66% homology to ZZA of an uncharacterized *P. pastoris* strain, and thus the promoters may be regulated by completely distinct mechanisms (paragraph bridging pages 5-6). The limited number of conserved sequences has not proven to be related to promoter function prior to the making of the instant invention (specification, page 6, lines 3-18). Thus, it is impossible for one to extrapolate from the few examples described herein those regulatory elements that would necessarily meet the structural/functional characteristics of the rejected claims.

"A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of regulatory elements, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

Given the very large genus of isolated polynucleotides encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the transcription factor binding sites within SEQ ID NOS: 16-21 that are required for regulatory function, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of polynucleotides. Thus, there is no structural/functional basis provided by the

Art Unit: 1636

prior art or instant specification for one of skill in the art to envision those polynucleotides that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 1-22.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Sears et al (Yeast, Vol. 14, pages 783-790, 1998; see the entire reference), as evidenced by GenBank Accession No. AF027961 (Publicly available 7/1/1998).

Sears et al teach expression plasmid pIB4, an isolated, double-stranded polynucleotide comprising an AOX1 promoter that contains a fragment of instant SEQ ID NO: 17, the entire sequence of instant SEQ ID NO: 18, the entire sequence of SEQ ID NO: 19, the entire sequence of SEQ ID NO: 20, and a fragment of SEQ ID NO: 21, and complements thereof (e.g. page 785, left column, 3rd full paragraph; Figure 1). Further, the sequence of pIB4 contains “a fragment” (i.e. one or two or more nucleotides) of SEQ ID NO: 16. GenBank Accession No. AF027961 is cited only to show that the nucleotide sequence of plasmid pIB4 contains the abovementioned sequences. See the attached alignments in Exhibits I-V. Sears et al teach plasmid pIB4-GUS, in which the GUS coding sequence was placed under the control of the AOX1 promoter (e.g. page 785, left column, last paragraph). The pIB4-GUS plasmid contains, in 5' to 3' order, the

Art Unit: 1636

abovementioned AOX1 promoter, the heterologous GUS coding region, and an AOX1 terminator sequence (e.g. page 785, left column, last paragraph; page 786, right column, last paragraph). Sears et al teach *Pichia pastoris* host cells comprising vector pIB4-GUS (e.g. page 786; page 788, second full paragraph). The GUS protein was expressed in the transformed yeast cells and partially isolated for enzyme assays (e.g. page 786; Table 2).

Claims 1-22 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Stroman et al (U.S. Patent No. 4,855,231, cited as reference 3 on the IDS filed 12/22/2003; see the entire reference), as evidenced by GenBank Accession No. I02097 (publicly available 5/21/1993).

Stroman et al teach an isolated DNA fragment comprising a regulatory region containing a nucleotide sequence less than about 1000 nucleotides which is 99% identical to instant SEQ ID NO: 16, and 100% identical to instant SEQ ID NOS: 17, 18, 19, 20, 21 and 31 (or the corresponding complements), which would hybridize under stringent conditions because of the identical sequence, and which is at least 80% sequence homology (actually 99 or 100% homology). See claims 3 and 19 of Stroman et al. GenBank I02097 is cited only to show that the nucleotide sequences disclosed in Stroman et al contain the abovementioned sequences. See the attached sequence comparison in Exhibits VI-XII. Moreover, Stroman et al teach plasmid pSAOH5, which contains instant SEQ ID NOS: 16-21 (e.g. Example XIV). This is the same plasmid used in the instant specification, and thus it would necessarily have the same sequence as the instant sequence identifiers. Stroman et al teach a recombinant vector comprising the DNA fragment (see the claims and the figures), an expression cassette comprising the DNA fragment operatively linked to a heterologous coding region (such as the lacZ gene), and a

Art Unit: 1636

termination sequence is taught (see the figures and claim 33, for example). A *Pichia pastoris* cell comprising the vector or expression cassette is taught (columns 67-68, for example). A method for the production of protein is taught comprising growing cells transformed with the vector or expression cassette so that the protein is expressed and isolating the expressed protein (column 67, for example).

Claims 1-20, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Buckholz (EP 0244598; see the entire reference).

Buckholz teaches an isolated DNA fragment comprising a regulatory region containing a nucleotide sequence less than about 1000 nucleotides which contains instant SEQ ID NOS: 16, 17, 18, 19, 20, 21 and 31 or a fragment thereof (or the corresponding complements), which would hybridize under stringent conditions because of the identical sequence to the instant sequences, and which is at least 80% sequence homology (actually 100% homology). See claims 1-3 and plasmid pSAOH5 in Figure 2. Plasmid pSAOH5 is the same plasmid used in the instant specification to isolate the AOX1 promoter sequences, and thus it would necessarily have the same sequence as the instant sequence identifiers. Buckholz teaches a recombinant vector comprising the DNA fragment (see page 4). An expression cassette comprising the DNA fragment operatively linked to a heterologous coding region (such as the lacZ gene) and a termination sequence is taught (see claims 4-5 and page 4). A *Pichia pastoris* cell comprising the vector or expression cassette is taught (page 4).

Buckholz teaches internal deletions of the AOX1 promoter such that the sequences are oriented relative to instant SEQ ID NO: 16 in a non-naturally occurring manner (e.g. page 6,

Art Unit: 1636

lines 1-29; Example II; Example V: Figures 1, 3 and 5). Based upon the teachings within the examples and the structure delineated in the Figures, the vectors disclosed at page 12, Table VII each contain SEQ ID NO: 16 and SEQ ID NO: 21 with variable internal deletions between the two sequences. For example, pBAZ604 contains SEQ ID NOS: 16, 17, 18, a fragment of 19, a fragment of 20, and 21; pBAZ601 and pBAZ603 contain SEQ ID NOS: 16, 17, a fragment of 18, a fragment of 20 and 21; pBAZ602 contains SEQ ID NOS: 16, a fragment of 17, a fragment of 20 and 21; and pBAZ801 and pBAZ802 contain SEQ ID NOS: 16, 17, 18, 19, a fragment of 20 and a fragment of 21.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Art Unit: 1636

Claims 26-29 rejected under 35 U.S.C. 103(a) as being unpatentable over Buckholz (EP 0244598; see the entire reference) in view of Romanos et al (Yeast, Vol. 8, pages 423-488, 1992, especially pages 454-461).

The teachings of Buckholz et al are described above and applied as before.

Buckholz et al do not teach an isolated nucleic acid comprising SEQ ID NO: 16 and at least one regulatory element of SEQ ID NO: 17, 18, 19 or 21 in a non-naturally occurring manner, wherein SEQ ID NO: 16, 17, 18 or 19 is present in more than one copy.

Romanos et al teach that vectors containing multiple expression cassettes are able to provide higher levels of heterologous protein expression in *P. pastoris* (e.g. page 455, right column, 1st full paragraph). Further, Romanos et al teach that the AOX1 promoter is capable of providing up to 30% of t.c.p. in *P. pastoris* in the presence of methanol (e.g. page 454, right column, 1st full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the isolated polynucleotide of Buckholz et al to include two expression cassettes each comprising the regulatory sequences taught in Table VII because Buckholz and Romanos et al teach it is within the ordinary skill in the art to use the AOX1 promoter in *P. pastoris* and Romanos et al teach it is within the skill of the art to make a vector comprising two expression cassettes. This modification would result in plasmids containing more than one copy of SEQ ID NO: 16, 17, 18 and/or 19.

One would have been motivated to make such a modification in order to receive the expected benefit of increased expression of the heterologous protein as taught by Romanos et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art,

Art Unit: 1636

and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Claim 23 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

jad

CELINE QIAN, PH.D.
PRIMARY EXAMINER

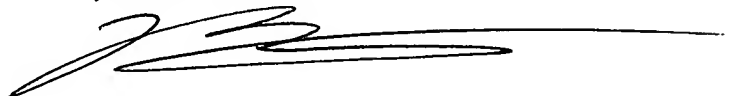


Exhibit I : AF027961 vs. SEQ ID NO: 17

**Blast 2 Sequences results**

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.14 [May-07-2006]

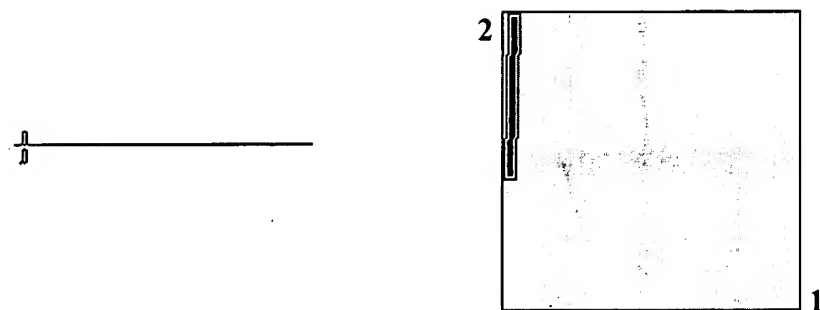
Match: Mismatch: gap open: gap extension:
x_dropoff: expect: wordsize: Filter ☒ View option
Masking character option Masking color option
☐ Show CDS translation

Sequence 1: [gi|2623126|gb|AF027961.1|AF027961](#)

Length = 5796 (1 .. 5796)

Sequence 2: [lcl|17](#)

Length = 140 (1 .. 140)



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.



Score = 150 bits (78), Expect = 5e-32
Identities = 78/78 (100%), Gaps = 0/78 (0%)
Strand=Plus/Plus

Query	187	CGCTCATTCCAATTCCTTCTATTAGGCTACTAACACCATGACTTTATTAGCCTGTCTATC	246
Sbjct	63	CGCTCATTCCAATTCCTTCTATTAGGCTACTAACACCATGACTTTATTAGCCTGTCTATC	122
Query	247	CTGGCCCCCCTGGCGAGG	264
Sbjct	123	CTGGCCCCCCTGGCGAGG	140

CPU time: 0.02 user secs. 0.02 sys. secs 0.04 total secs.

Lambda	K	H
1.33	0.621	1.12

Gapped

Lambda	K	H
1.33	0.621	1.12

Matrix: blastn matrix:1 -2

Gap Penalties: Existence: 5, Extension: 2

Number of Sequences: 1

Number of Hits to DB: 26

Number of extensions: 1

Number of successful extensions: 1

Number of sequences better than 10.0: 1

Number of HSP's gapped: 1

Number of HSP's successfully gapped: 1

Length of query: 5796

Length of database: 18,602,024,809

Length adjustment: 28

Effective length of query: 5768

Effective length of database: 18,602,024,781

Effective search space: 107296478936808

Effective search space used: 107296478936808

X1: 10 (19.2 bits)

X2: 26 (50.0 bits)

X3: 26 (50.0 bits)

S1: 10 (19.9 bits)

S2: 23 (44.9 bits)

Exhibit II : AF027961 vs. SEQ ID NO: 18

**Blast 2 Sequences results**

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.14 [May-07-2006]

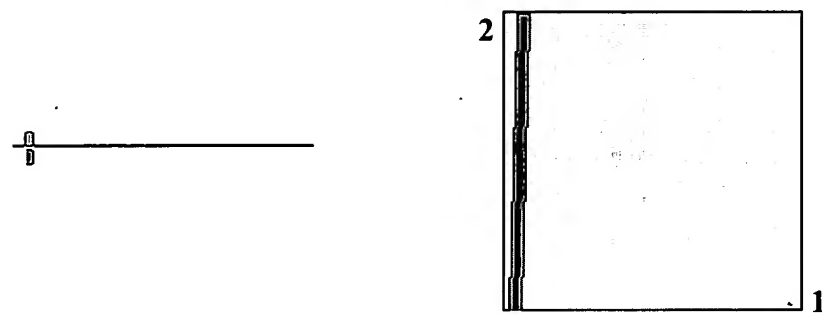
Match: Mismatch: gap open: gap extension:
x_dropoff: expect: wordsize: Filter ☒ View option
Masking character option Masking color option
☐ Show CDS translation

Sequence 1: [gi|2623126|gb|AF027961.1|AF027961](#)

Length = 5796 (1 .. 5796)

Sequence 2: [lcl|18](#)

Length = 139 (1 .. 139)



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.



Score = 267 bits (139), Expect = 2e-67
Identities = 139/139 (100%), Gaps = 0/139 (0%)
Strand=Plus/Plus

Query	265	TCATGTTTGTGTTATTTCCGAATGCAACAAGCTCCGCATTACACCCGAACATCACTCCAGA	324
Sbjct	1	TCATGTTTGTGTTATTTCCGAATGCAACAAGCTCCGCATTACACCCGAACATCACTCCAGA	60
Query	325	TGAGGGCTTTCTGAGTGTGGGGTCAAATAGTTTCATGTTCCCAAATGGCCCAAACTGAC	384
Sbjct	61	TGAGGGCTTTCTGAGTGTGGGGTCAAATAGTTTCATGTTCCCAAATGGCCCAAACTGAC	120
Query	385	AGTTTAAACGCTGTCTTGG	403

Sbjct 121 AGTTTAAACGCTGTCTTGG 139

CPU time: 0.02 user secs. 0.00 sys. secs 0.02 total secs.

Lambda	K	H
1.33	0.621	1.12

Gapped

Lambda	K	H
1.33	0.621	1.12

Matrix: blastn matrix:1 -2
Gap Penalties: Existence: 5, Extension: 2
Number of Sequences: 1
Number of Hits to DB: 37
Number of extensions: 2
Number of successful extensions: 2
Number of sequences better than 10.0: 1
Number of HSP's gapped: 2
Number of HSP's successfully gapped: 1
Length of query: 5796
Length of database: 18,602,024,809
Length adjustment: 28
Effective length of query: 5768
Effective length of database: 18,602,024,781
Effective search space: 107296478936808
Effective search space used: 107296478936808
X1: 10 (19.2 bits)
X2: 26 (50.0 bits)
X3: 26 (50.0 bits)
S1: 10 (19.9 bits)
S2: 23 (44.9 bits)

Exhibit III : AF027961 vs. SEQ ID NO:19

**Blast 2 Sequences results**

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.14 [May-07-2006]

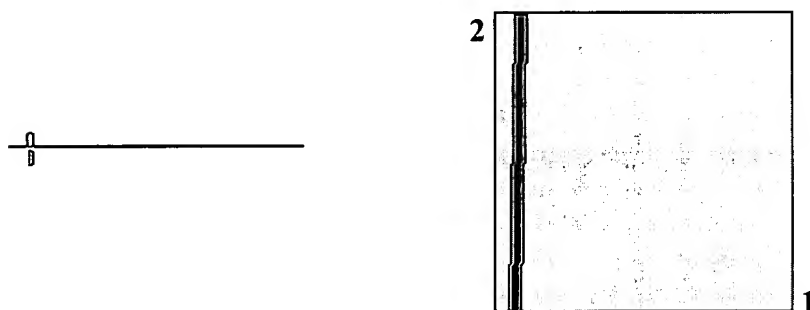
Match: Mismatch: gap open: gap extension:
x_dropoff: expect: wordsize: Filter ☒ View option
Masking character option Masking color option
☐ Show CDS translation

Sequence 1: [gi|2623126|gb|AF027961.1|AF027961](#)

Length = 5796 (1 .. 5796)

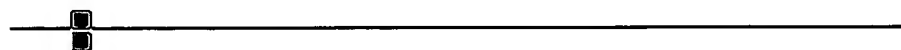
Sequence 2: [lcl|19](#)

Length = 127 (1 .. 127)



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.



Score = 239 bits (124), Expect = 1e-58
Identities = 126/127 (99%), Gaps = 0/127 (0%)
Strand=Plus/Plus

Query	404	AACCTAATATGACAAAAGCGTGATCTCATCCAAGATGAACTAAGTTTGGTTCGTTGAAAT	463
Sbjct	1	AACCTAATATGACAAAAGCGTGATCTCATCCAAGATGAACTAAGTTTGGTTCGTTGAAAT	60
Query	464	GCTAACGGCCAGTTGGTCAAAAAGAACTTCCAAAAGTCGCCATACCGTTTGTCTTGTTT	523
Sbjct	61	CCTAACGGCCAGTTGGTCAAAAAGAACTTCCAAAAGTCGCCATACCGTTTGTCTTGTTT	120
Query	524	GGTATTG	530

Sbjct 121 GGTATTG 127

CPU time: 0.02 user secs. 0.00 sys. secs 0.02 total secs.

Lambda	K	H
1.33	0.621	1.12

Gapped

Lambda	K	H
1.33	0.621	1.12

Matrix: blastn matrix:1 -2

Gap Penalties: Existence: 5, Extension: 2

Number of Sequences: 1

Number of Hits to DB: 37

Number of extensions: 1

Number of successful extensions: 1

Number of sequences better than 10.0: 1

Number of HSP's gapped: 1

Number of HSP's successfully gapped: 1

Length of query: 5796

Length of database: 18,602,024,809

Length adjustment: 28

Effective length of query: 5768

Effective length of database: 18,602,024,781

Effective search space: 107296478936808

Effective search space used: 107296478936808

X1: 10 (19.2 bits)

X2: 26 (50.0 bits)

X3: 26 (50.0 bits)

S1: 10 (19.9 bits)

S2: 23 (44.9 bits)

Exhibit IV : AF027961 vs. SEQ ID NO: 20

**Blast 2 Sequences results**

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.14 [May-07-2006]

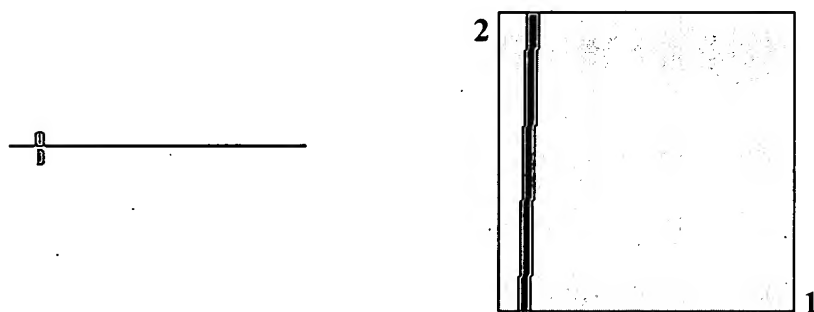
Match: Mismatch: gap open: gap extension:
x_dropoff: expect: wordsize: Filter ☒ View option
Masking character option Masking color option
☐ Show CDS translation

Sequence 1: [gi|2623126|gb|AF027961.1|AF027961](#)

Length = 5796 (1 .. 5796)

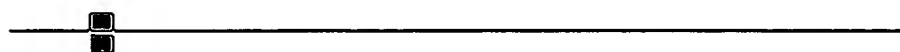
Sequence 2: [lcl|20](#)

Length = 151 (1 .. 151)



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.



Score = 291 bits (151), Expect = 3e-74
Identities = 151/151 (100%), Gaps = 0/151 (0%)
Strand=Plus/Plus

Query	531	ATTGACGAATGCTCAAAAATAATCTCATTAATGCTTAGCGCAGTCTCTCTATCGCTTCTG	590
Sbjct	1	ATTGACGAATGCTCAAAAATAATCTCATTAATGCTTAGCGCAGTCTCTCTATCGCTTCTG	60
Query	591	AACCCGGTGGCACCTGTGCCGAAACGCAAATGGGGAAACAACCCGCTTTTGGATGATTA	650
Sbjct	61	AACCCGGTGGCACCTGTGCCGAAACGCAAATGGGGAAACAACCCGCTTTTGGATGATTA	120
Query	651	TGCATTGTCCTCCACATTGTATGCTTCCAAG	681

Sbjct 121 TGCATTGTCCTCCACATTGTATGCTTCCAAG 151

CPU time: 0.02 user secs. 0.00 sys. secs 0.02 total secs.

Lambda	K	H
1.33	0.621	1.12

Gapped

Lambda	K	H
1.33	0.621	1.12

Matrix: blastn matrix:1 -2
Gap Penalties: Existence: 5, Extension: 2
Number of Sequences: 1
Number of Hits to DB: 43
Number of extensions: 1
Number of successful extensions: 1
Number of sequences better than 10.0: 1
Number of HSP's gapped: 1
Number of HSP's successfully gapped: 1
Length of query: 5796
Length of database: 18,602,024,809
Length adjustment: 28
Effective length of query: 5768
Effective length of database: 18,602,024,781
Effective search space: 107296478936808
Effective search space used: 107296478936808
X1: 10 (19.2 bits)
X2: 26 (50.0 bits)
X3: 26 (50.0 bits)
S1: 10 (19.9 bits)
S2: 23 (44.9 bits)



Blast 2 Sequences results

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.14 [May-07-2006]

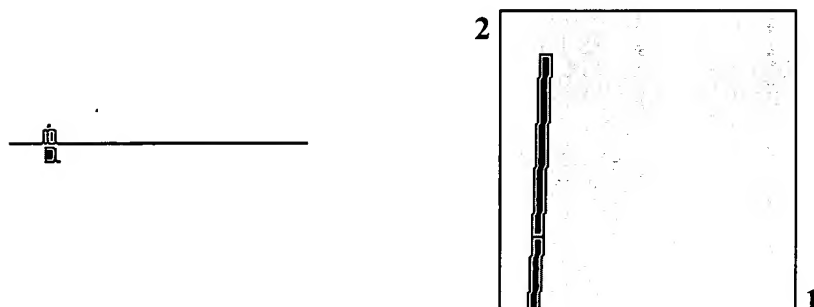
Match: Mismatch: gap open: gap extension:
x_dropoff: expect: wordsize: Filter ☐ View option
Masking character option Masking color option
☐ Show CDS translation

Sequence 1: gi|2623126|gb|AF027961.1|AF027961

Length = 5796 (1 .. 5796)

Sequence 2: lcl|21

Length = 282 (1 .. 282)



NOTE:Bitscore and expect value are calculated based on the size of the nr database.

NOTE:If protein translation is reversed, please repeat the search with reverse strand of the query sequence.

Score = 446 bits (232), Expect = 4e-121
Identities = 239/240 (99%), Gaps = 1/240 (0%)
Strand=Plus/Plus

Query	682	ATTCTGGTGGGAATACTGCTGATAGCCTAACGTTTCATGATCAAATTTAACTGTTCTAAC	741
Sbjct	1	ATTCTGGTGGGAATACTGCTGATAGCCTAACGTTTCATGATCAAATTTAACTGTTCTAAC	60
Query	742	CCCTACTTG-ACAGGCAATATATAAACAGAAGGAAGCTGCCCTGTCTTAAACCTTTTTTT	800
Sbjct	61	CCCTACTTGGACAGGCAATATATAAACAGAAGGAAGCTGCCCTGTCTTAAACCTTTTTTT	120
Query	801	TTATCATCATTATTAGCTTACTTTTCATAATTGCGACTGGTTCCAATTGACAAGCTTTTGA	860

```
Sbjct 121 TTATCATCATTATTAGCTTACTTTTCATAATTGCGACTGGTTCCAATTGACAAGCTTTTGA 180
Query 861 TTTTAACGACTTTTAACGACAACCTTGAGAAGATCAAAAAACAATAATTATTCGAAACGA 920
          |||
Sbjct 181 TTTTAACGACTTTTAACGACAACCTTGAGAAGATCAAAAAACAATAATTATTCGAAACGA 240
```

CPU time: 0.02 user secs. 0.00 sys. secs 0.02 total secs.

Lambda	K	H
1.33	0.621	1.12

Gapped

Lambda	K	H
1.33	0.621	1.12

Matrix: blastn matrix:1 -2
Gap Penalties: Existence: 5, Extension: 2
Number of Sequences: 1
Number of Hits to DB: 73
Number of extensions: 3
Number of successful extensions: 3
Number of sequences better than 10.0: 1
Number of HSP's gapped: 2
Number of HSP's successfully gapped: 1
Length of query: 5796
Length of database: 18,602,024,809
Length adjustment: 28
Effective length of query: 5768
Effective length of database: 18,602,024,781
Effective search space: 107296478936808
Effective search space used: 107296478936808
X1: 11 (21.1 bits)
X2: 26 (50.0 bits)
X3: 26 (50.0 bits)
S1: 11 (21.8 bits)
S2: 23 (44.9 bits)

Exhibit VI : SEQ ID NO: 31 vs. US 4,855,231

>gi|270257|gb|I02097.1| Sequence 5 from Patent US 4855231
Length=927

Score = 1530 bits (772), Expect = 0.0
Identities = 799/799 (100%), Gaps = 0/799 (0%)
Strand=Plus/Plus

Query	1	AGGACTCATCCTCTTCTCTAACACCATTTTGCATGAAAACAGCCAGTTATGGGCTTGATG	60
Sbjct	129	AGGACTCATCCTCTTCTCTAACACCATTTTGCATGAAAACAGCCAGTTATGGGCTTGATG	188
Query	61	GAGCTCGCTCATTCCAATTCCTTCTATTAGGCTACTAACACCATGACTTTATTAGCCTGT	120
Sbjct	189	GAGCTCGCTCATTCCAATTCCTTCTATTAGGCTACTAACACCATGACTTTATTAGCCTGT	248
Query	121	CTATCCTGGCCCCCTGGCGAGGTCATGTTTGTGTTATTTCCGAATGCAACAAGCTCCGCA	180
Sbjct	249	CTATCCTGGCCCCCTGGCGAGGTCATGTTTGTGTTATTTCCGAATGCAACAAGCTCCGCA	308
Query	181	TTACACCCGAACATCACTCCAGATGAGGGCTTTCTGAGTGTGGGGTCAAATAGTTTCATG	240
Sbjct	309	TTACACCCGAACATCACTCCAGATGAGGGCTTTCTGAGTGTGGGGTCAAATAGTTTCATG	368
Query	241	TTCCCAAATGGCCCCAAACTGACAGTTTAAACGCTGTCTTGGAACCTAATATGACAAAAG	300
Sbjct	369	TTCCCAAATGGCCCCAAACTGACAGTTTAAACGCTGTCTTGGAACCTAATATGACAAAAG	428
Query	301	CGTGATCTCATCCAAGATGAACTAAGTTTGGTTCGTTGAAATCCTAACGGCCAGTTGGTC	360
Sbjct	429	CGTGATCTCATCCAAGATGAACTAAGTTTGGTTCGTTGAAATCCTAACGGCCAGTTGGTC	488
Query	361	AAAAAGAACTTCCAAAAGTCGCCATACCGTTTGTCTTGTTTGGTATTGATTGACGAATG	420
Sbjct	489	AAAAAGAACTTCCAAAAGTCGCCATACCGTTTGTCTTGTTTGGTATTGATTGACGAATG	548
Query	421	CTCAAAAATAATCTCATTAAATGCTTAGCGCAGTCTCTCTATCGCTTCTGAACCCGGTGGC	480
Sbjct	549	CTCAAAAATAATCTCATTAAATGCTTAGCGCAGTCTCTCTATCGCTTCTGAACCCGGTGGC	608
Query	481	ACCTGTGCCGAAACGCAAATGGGGAAACAACCCGCTTTTGGATGATTATGCATTGTCCT	540
Sbjct	609	ACCTGTGCCGAAACGCAAATGGGGAAACAACCCGCTTTTGGATGATTATGCATTGTCCT	668
Query	541	CCACATTGTATGCTTCCAAGATTCTGGTGGGAATACTGCTGATAGCCTAACGTTTCATGAT	600
Sbjct	669	CCACATTGTATGCTTCCAAGATTCTGGTGGGAATACTGCTGATAGCCTAACGTTTCATGAT	728
Query	601	CAAAATTTAACTGTTCTAACCCCTACTTGGACAGGCAATATATAAACAGAAGGAAGCTGC	660
Sbjct	729	CAAAATTTAACTGTTCTAACCCCTACTTGGACAGGCAATATATAAACAGAAGGAAGCTGC	788
Query	661	CCTGTCTTAAACCTtttttttttATCATCATTATTAGCTTACTTTTCATAATTGCGACTGGT	720
Sbjct	789	CCTGTCTTAAACCTTTTTTTTTTATCATCATTATTAGCTTACTTTTCATAATTGCGACTGGT	848
Query	721	TCCAATTGACAAGCTTTTGATTTTAAACGACTTTTAAACGACAACCTTGAGAAGATCAAAAAA	780
Sbjct	849	TCCAATTGACAAGCTTTTGATTTTAAACGACTTTTAAACGACAACCTTGAGAAGATCAAAAAA	908
Query	781	CAACTAATTATTCGAAACG	799

```
          |||||
Sbjct  909  CAACTAATTATTCGAAACG  927
```

Exhibit VII: I02097 vs. SEQ ID NO116



Blast 2 Sequences results

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.14 [May-07-2006]

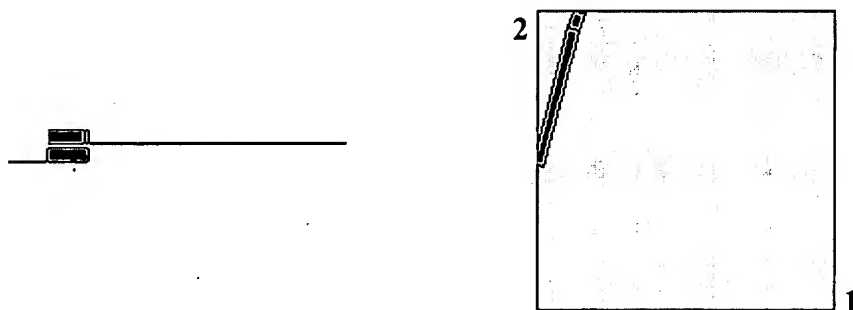
Match: Mismatch: gap open: gap extension:
 x_dropoff: expect: wordsize: Filter ☐ View option
 Masking character option Masking color option
☐ Show CDS translation

Sequence 1: gi|270257|gb|I02097.1|

Length = 927 (1 .. 927)

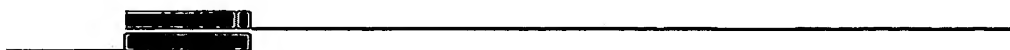
Sequence 2: lcl|16

Length = 256 (1 .. 256)



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.



Score = 239 bits (124), Expect = 2e-59
 Identities = 131/132 (99%), Gaps = 1/132 (0%)
 Strand=Plus/Plus

Query	1	AGATCTAACATCCAAAGACGAAAGGTTGAATGAAACCTTTTGGCCATCCGACATCCACAG	60
Sbjct	125	AGATCTAACATCCAAAGACGAAAGGTTGAATGAAACCTTTTGGCCATCCGACATCCACAG	184
Query	61	GTCCATTCTCACACATAAGTGCCAAACGCAACAGGAGGGGATACACTAGCAGCAGA-CGT	119
Sbjct	185	GTCCATTCTCACACATAAGTGCCAAACGCAACAGGAGGGGATACACTAGCAGCAGACCCT	244
Query	120	TGCAAACGCAGG	131

Sbjct 245 TGCAAACGCAGG 256

CPU time: 0.02 user secs. 0.00 sys. secs 0.02 total secs.

Lambda	K	H
1.33	0.621	1.12

Gapped

Lambda	K	H
1.33	0.621	1.12

Matrix: blastn matrix:1 -2

Gap Penalties: Existence: 5, Extension: 2

Number of Sequences: 1

Number of Hits to DB: 36

Number of extensions: 2

Number of successful extensions: 2

Number of sequences better than 10.0: 1

Number of HSP's gapped: 1

Number of HSP's successfully gapped: 1

Length of query: 927

Length of database: 18,602,024,809

Length adjustment: 26

Effective length of query: 901

Effective length of database: 18,602,024,783

Effective search space: 16760424329483

Effective search space used: 16760424329483

X1: 11 (21.1 bits)

X2: 26 (50.0 bits)

X3: 26 (50.0 bits)

S1: 11 (21.8 bits)

S2: 21 (41.1 bits)

Exhibit VIII IO2097 vs. SEQ ID NO:17

**Blast 2 Sequences results**

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.14 [May-07-2006]

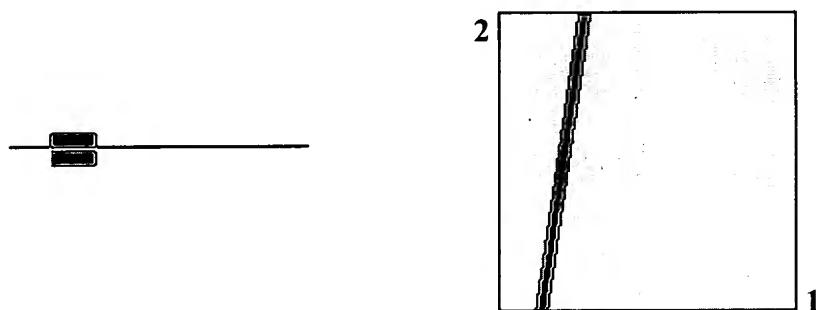
Match: Mismatch: gap open: gap extension:
x_dropoff: expect: wordsize: Filter ☒ View option
Masking character option Masking color option
☐ Show CDS translation

Sequence 1: gi|270257|gb|IO2097.1|

Length = 927 (1 .. 927)

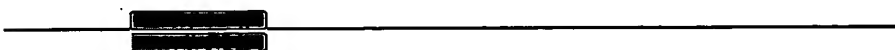
Sequence 2: lcl|17

Length = 140 (1 .. 140)



NOTE:Bitscore and expect value are calculated based on the size of the nr database.

NOTE:If protein translation is reversed, please repeat the search with reverse strand of the query sequence.



Score = 269 bits (140), Expect = 1e-68
Identities = 140/140 (100%), Gaps = 0/140 (0%)
Strand=Plus/Plus

Query	132	ACTCATCTCTTCTCTAACACCATTTTGCATGAAAACAGCCAGTTATGGGCTTGATGGAG	191
Sbjct	1	ACTCATCTCTTCTCTAACACCATTTTGCATGAAAACAGCCAGTTATGGGCTTGATGGAG	60
Query	192	CTCGCTCATTCCAATTCCTTCTATTAGGCTACTAACACCATGACTTTATTAGCCTGTCTA	251
Sbjct	61	CTCGCTCATTCCAATTCCTTCTATTAGGCTACTAACACCATGACTTTATTAGCCTGTCTA	120
Query	252	TCCTGGCCCCCTGGCGAGG	271

Sbjct 121 TCCTGGCCCCCCTGGCGAGG 140

CPU time: 0.01 user secs. 0.00 sys. secs 0.01 total secs.

Lambda	K	H
1.33	0.621	1.12

Gapped

Lambda	K	H
1.33	0.621	1.12

Matrix: blastn matrix:1 -2

Gap Penalties: Existence: 5, Extension: 2

Number of Sequences: 1

Number of Hits to DB: 37

Number of extensions: 1

Number of successful extensions: 1

Number of sequences better than 10.0: 1

Number of HSP's gapped: 1

Number of HSP's successfully gapped: 1

Length of query: 927

Length of database: 18,602,024,809

Length adjustment: 26

Effective length of query: 901

Effective length of database: 18,602,024,783

Effective search space: 16760424329483

Effective search space used: 16760424329483

X1: 10 (19.2 bits)

X2: 26 (50.0 bits)

X3: 26 (50.0 bits)

S1: 10 (19.9 bits)

S2: 21 (41.1 bits)



Blast 2 Sequences results

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.14 [May-07-2006]

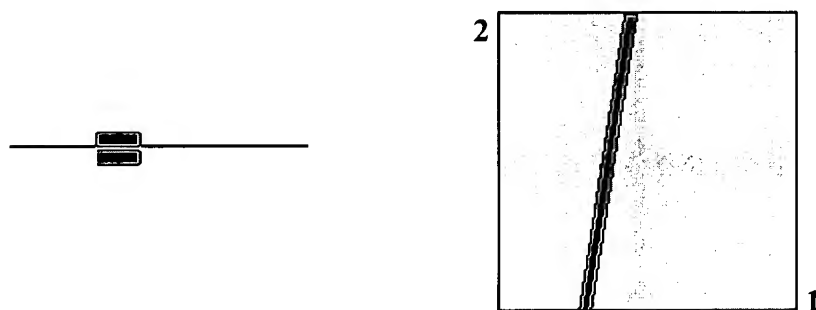
Match: Mismatch: gap open: gap extension:
 x_dropoff: expect: wordsize: Filter ☒ View option
 Masking character option Masking color option
☐ Show CDS translation

Sequence 1: [gi|270257|gb|I02097.1|](#)

Length = 927 (1 .. 927)

Sequence 2: [lcl|18](#)

Length = 139 (1 .. 139)



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.

Score = 267 bits (139), Expect = 4e-68
 Identities = 139/139 (100%), Gaps = 0/139 (0%)
 Strand=Plus/Plus

Query	272	TCATGTTTGTGTTATTTCCGAATGCAACAAGCTCCGCATTACACCCGAACATCACTCCAGA	331
Sbjct	1	TCATGTTTGTGTTATTTCCGAATGCAACAAGCTCCGCATTACACCCGAACATCACTCCAGA	60
Query	332	TGAGGGCTTTCTGAGTGTGGGGTCAAATAGTTTCATGTTCCCAAATGGCCCAAACTGAC	391
Sbjct	61	TGAGGGCTTTCTGAGTGTGGGGTCAAATAGTTTCATGTTCCCAAATGGCCCAAACTGAC	120
Query	392	AGTTTAAACGCTGTCTTGG	410

Sbjct 121 AGTTTAAACGCTGTCTTGG 139

CPU time: 0.02 user secs. 0.00 sys. secs 0.02 total secs.

Lambda	K	H
1.33	0.621	1.12

Gapped

Lambda	K	H
1.33	0.621	1.12

Matrix: blastn matrix:1 -2

Gap Penalties: Existence: 5, Extension: 2

Number of Sequences: 1

Number of Hits to DB: 33

Number of extensions: 1

Number of successful extensions: 1

Number of sequences better than 10.0: 1

Number of HSP's gapped: 1

Number of HSP's successfully gapped: 1

Length of query: 927

Length of database: 18,602,024,809

Length adjustment: 26

Effective length of query: 901

Effective length of database: 18,602,024,783

Effective search space: 16760424329483

Effective search space used: 16760424329483

X1: 10 (19.2 bits)

X2: 26 (50.0 bits)

X3: 26 (50.0 bits)

S1: 10 (19.9 bits)

S2: 21 (41.1 bits)

Exhibit X

I02097 vs. SEQ ID NO:19

**Blast 2 Sequences results**

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.14 [May-07-2006]

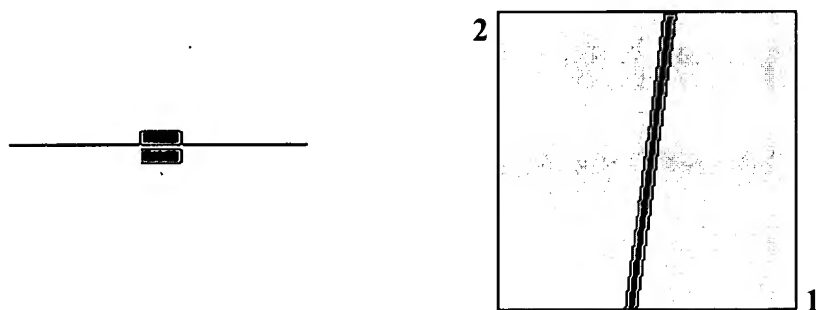
Match: Mismatch: gap open: gap extension:
x_dropoff: expect: wordsize: Filter ☐ View option
Masking character option Masking color option
☐ Show CDS translation

Sequence 1: gi|270257|gb|I02097.1|

Length = 927 (1 .. 927)

Sequence 2: lcl|19

Length = 127 (1 .. 127)



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.



Score = 244 bits (127), Expect = 3e-61
Identities = 127/127 (100%), Gaps = 0/127 (0%)
Strand=Plus/Plus

Query	411	AACCTAATATGACAAAAGCGTGATCTCATCCAAGATGAACTAAGTTTGGTTCGTTGAAAT	470.
Sbjct	1	AACCTAATATGACAAAAGCGTGATCTCATCCAAGATGAACTAAGTTTGGTTCGTTGAAAT	60
Query	471	CCTAACGGCCAGTTGGTCAAAAAGAACTTCCAAAAGTCGCCATACCGTTTGTCTTGTTT	530
Sbjct	61	CCTAACGGCCAGTTGGTCAAAAAGAACTTCCAAAAGTCGCCATACCGTTTGTCTTGTTT	120
Query	531	GGTATTG	537

Sbjct 121 GGTATTG 127

CPU time: 0.01 user secs. 0.01 sys. secs 0.02 total secs.

Lambda	K	H
1.33	0.621	1.12

Gapped

Lambda	K	H
1.33	0.621	1.12

Matrix: blastn matrix:1 -2
Gap Penalties: Existence: 5, Extension: 2
Number of Sequences: 1
Number of Hits to DB: 32
Number of extensions: 1
Number of successful extensions: 1
Number of sequences better than 10.0: 1
Number of HSP's gapped: 1
Number of HSP's successfully gapped: 1
Length of query: 927
Length of database: 18,602,024,809
Length adjustment: 26
Effective length of query: 901
Effective length of database: 18,602,024,783
Effective search space: 16760424329483
Effective search space used: 16760424329483
X1: 10 (19.2 bits)
X2: 26 (50.0 bits)
X3: 26 (50.0 bits)
S1: 10 (19.9 bits)
S2: 21 (41.1 bits)

Exhibit XI

I02097 vs. SEQ ID NO:20



Blast 2 Sequences results

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.14 [May-07-2006]

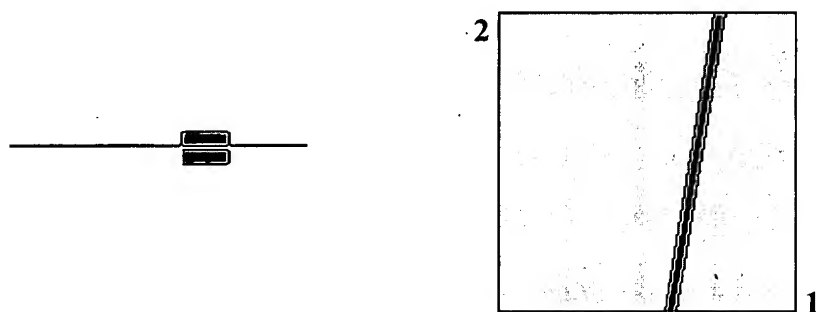
Match: Mismatch: gap open: gap extension:
 x_dropoff: expect: wordsize: Filter ☐ View option
 Masking character option Masking color option
☐ Show CDS translation

Sequence 1: gi|270257|gb|I02097.1|

Length = 927 (1 .. 927)

Sequence 2: lcl|20

Length = 151 (1 .. 151)



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.

Score = 291 bits (151), Expect = 4e-75
 Identities = 151/151 (100%), Gaps = 0/151 (0%)
 Strand=Plus/Plus

```

Query  538  ATTGACGAATGCTCAAAAATAATCTCATTAATGCTTAGCGCAGTCTCTCTATCGCTTCTG  597
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct   1    ATTGACGAATGCTCAAAAATAATCTCATTAATGCTTAGCGCAGTCTCTCTATCGCTTCTG   60

Query  598  AACCCGGTGGCACCTGTGCCGAAACGCAAATGGGGAAACAACCCGCTTTTGGATGATTA  657
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct   61  AACCCGGTGGCACCTGTGCCGAAACGCAAATGGGGAAACAACCCGCTTTTGGATGATTA  120

Query  658  TGCATTGTCCTCCACATTGTATGCTTCCAAG  688
          ||||||||||||||||||||||||||||
  
```

Sbjct 121 TGCATTGTCCTCCACATTGTATGCTTCCAAG 151

CPU time: 0.01 user secs. 0.02 sys. secs 0.03 total secs.

Lambda	K	H
1.33	0.621	1.12

Gapped

Lambda	K	H
1.33	0.621	1.12

Matrix: blastn matrix:1 -2

Gap Penalties: Existence: 5, Extension: 2

Number of Sequences: 1

Number of Hits to DB: 37

Number of extensions: 1

Number of successful extensions: 1

Number of sequences better than 10.0: 1

Number of HSP's gapped: 1

Number of HSP's successfully gapped: 1

Length of query: 927

Length of database: 18,602,024,809

Length adjustment: 26

Effective length of query: 901

Effective length of database: 18,602,024,783

Effective search space: 16760424329483

Effective search space used: 16760424329483

X1: 10 (19.2 bits)

X2: 26 (50.0 bits)

X3: 26 (50.0 bits)

S1: 10 (19.9 bits)

S2: 21 (41.1 bits)



Blast 2 Sequences results

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.14 [May-07-2006]

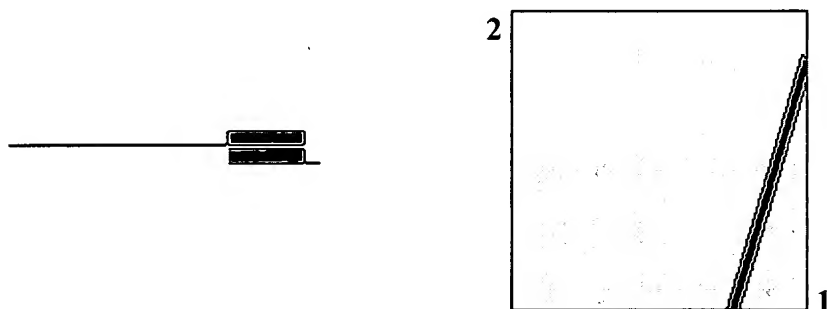
Match: Mismatch: gap open: gap extension:
 x_dropoff: expect: wordsize: Filter ☐ View option
 Masking character option Masking color option
☐ Show CDS translation

Sequence 1: [gi|270257|gb|I02097.1|](#)

Length = 927 (1 .. 927)

Sequence 2: [lc|21](#)

Length = 282 (1 .. 282)



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.

Score = 460 bits (239), Expect = 5e-126
 Identities = 239/239 (100%), Gaps = 0/239 (0%)
 Strand=Plus/Plus

Query	689	ATTCTGGTGGGAATACTGCTGATAGCCTAACGTTTCATGATCAAATTTAACTGTTCTAAC	748
Sbjct	1	ATTCTGGTGGGAATACTGCTGATAGCCTAACGTTTCATGATCAAATTTAACTGTTCTAAC	60
Query	749	CCCTACTTGGACAGGCAATATATAAACAGAAGGAAGCTGCCCTGTCTTAAACCTTTTTTT	808
Sbjct	61	CCCTACTTGGACAGGCAATATATAAACAGAAGGAAGCTGCCCTGTCTTAAACCTTTTTTT	120
Query	809	TTATCATCATTATTAGCTTACTTTTCATAATTGCGACTGGTTCCAATTGACAAGCTTTTGA	868

```
Sbjct 121 TTATCATCATTATTAGCTTACTTTTCATAATTGCGACTGGTTCCAATTGACAAGCTTTTGA 180
Query 869 TTTTAACGACTTTTAACGACAACCTTGAGAAGATCAAAAAACAATAATTATTCGAAACG 927
          |||
Sbjct 181 TTTTAACGACTTTTAACGACAACCTTGAGAAGATCAAAAAACAATAATTATTCGAAACG 239
```

CPU time: 0.01 user secs. 0.01 sys. secs 0.02 total secs.

Lambda K H
1.33 0.621 1.12

Gapped
Lambda K H
1.33 0.621 1.12

Matrix: blastn matrix:1 -2
Gap Penalties: Existence: 5, Extension: 2
Number of Sequences: 1
Number of Hits to DB: 61
Number of extensions: 1
Number of successful extensions: 1
Number of sequences better than 10.0: 1
Number of HSP's gapped: 1
Number of HSP's successfully gapped: 1
Length of query: 927
Length of database: 18,602,024,809
Length adjustment: 26
Effective length of query: 901
Effective length of database: 18,602,024,783
Effective search space: 16760424329483
Effective search space used: 16760424329483
X1: 11 (21.1 bits)
X2: 26 (50.0 bits)
X3: 26 (50.0 bits)
S1: 11 (21.8 bits)
S2: 21 (41.1 bits)